AR201-14065

Sarah_Loftus@americanchemistry.com on 11/11/2002 08:38:01 AM

To: Rtk Chem/DC/USEPA/US@EPA, NCIC OPPT/DC/USEPA/US@EPA
cc:

Subject: Group 4 HPV Test Plan Submission

HPV Test Plan Submission from the American Chemistry Council Petroleum Additives HERTG - HPV Registration Number

Three documents (1. cover letter, 2. test plan and 3. robust summaries) are attached to this e-mail for the HERTG HPV Dithiophoshate category. If you have any questions or comments, please feel free to contact me. Below, my contact information is listed. Thank you very much. Sarah McLallen

(See attached file: Group 4 (All Docs).zip)

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- Group 4 (All Docs).zip

November 11, 2002

By Mail
Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program – Test Plan Submission from HERTG
Registration Number

Dear Administrator Whitman:

The American Chemistry Council Petroleum Additives Panel (Panel) Health, Environmental, and Regulatory Task Group (HERTG) submits for review and public comment its test plan report, as well as related robust summaries, for the *"Dithiophosphate Alkyl Esters"* category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The HERTG understands that there will be a 120-day review period for the test plan report and that all comments generated by or provided to EPA will be forwarded to the HERTG for consideration.

The dithiophosphate alkyl esters in this category are site limited intermediates, which are used as petroleum lubricant additives, are characterized by having structural similarities and limited reactivity, low biological activity, and very low water solubility. Based upon the data reviewed in the attached report, the HERTG concludes that the physicochemical and toxicological properties of the proposed dithiophosphate alkyl esters category members are similar and follow a regular pattern as a result of structural similarity. Thus, HERTG believes these nine chemicals meet the EPA definition of a chemical category and will test them in accordance with the test plan summarized in the attached report. The nine chemicals in the dithiophosphate alkyl esters category are as follows:

- Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters – (CAS # 84605-28-7), referred to as "mixed 1,3-dimethylbutyl and iso-propyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters – (CAS # 68516-01-8), referred to as "mixed isobutyl and pentyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters – (CAS # 68784-30-5), referred to as "mixed sec-butyl and 1,3-dimethylbutyl derivative"
- Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters – (CAS # 113706-14-2), referred to as "mixed sec-butyl and isooctyl derivative"

- Phosphorodithioic acid, mixed 0,0-bis(2-ethylhexyl and iso-butyl) esters – (CAS # 68784-32-7), referred to as "mixed 2-ethylhexyl and isobutyl derivative"
- 2-Pentanol, 4-methyl-hydrogen phosphorodithioate – (CAS # 6028-47-3), referred to as "1,3-dimethylbutyl derivative"
- Phosphorodithioic acid, 0,0-bis(2-ethylhexyl) esters – (CAS# 5810-88-8), referred to as "2-ethylhexyl derivative"
- Phosphorodithioic acid, O,O-dioctyl ester, branched – (CAS# 68649-43-4), referred to as "branched isooctyl derivative"
- Phosphorodithioic acid, O,O-diisooctyl ester – (CAS# 26999-29-1), referred to as "isooctyl derivative"

Briefly, the test plan for the HERTG dithiophosphate alkyl esters category includes the following tests and computer modeling:

- Water solubility – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Photodegradation (atmospheric oxidation) modeling – Data will be developed using the AOP model in EPIWIN (1999). [EPIWIN. (1999). Estimation Program Interface for Windows, version 3.04. Syracuse Research Corporation, Syracuse, NY, USA.]
- Fugacity modeling – Environmental partitioning will be developed using a Mackay Level I (1998) equilibrium partitioning model. [Mackay, D. (1998). Level I Fugacity-Based Environmental Equilibrium Partitioning Model, Version 2.1 (16-bit). Environmental Modeling Centre, Trent University, Ontario, Canada.] and provided in robust summaries.
- Acute fish toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Acute invertebrate toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Alga toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Mutagenicity – Bacterial mutation and *in vitro* chromosome aberration studies will be conducted on mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.

As HERTG developed this test plan, HERTG considered carefully and tried to limit how many animals might be required for tests included in the proposed plan and conditions to which the animals might be exposed. As noted above, a minimal amount of animal testing is proposed. HERTG believes that the concerns of some non-governmental organizations about animal welfare have been fully considered and that use of animals in this proposed test plan has been minimized.

Thank you in advance for your attention to this matter. If you have any questions regarding the test plan report or the robust summaries, or HERTG's activities associated with the Challenge Program, please contact Sarah Loftus McLallen at 703-741-5607 (telephone), 703-741-6091 (telefax) or Sarah_McLallen@americanchemistry.com (e-mail).

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

cc: HERTG members

AR201-14065A

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

TEST PLAN

For

DITHIOPHOSPHATE ALKYL ESTERS CATEGORY

Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental, and Regulatory Task Group

October 10, 2002

Dithiophosphate alkyl esters category
Group 4
October 10, 2002

LIST OF MEMBER COMPANIES IN THE HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

BP, plc.

Chevron Oronite Company, LLC

Crompton Corporation

Ethyl Corporation

ExxonMobil Chemical Company

Ferro Corporation

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

Rhodia, Inc. (formerly Albright & Wilson Americas Inc.)

EXECUTIVE SUMMARY

The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its member companies, hereby submit for review and public comment their test plan for the *"Dithiophosphate alkyl esters"* category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program. This report should be read in its entirety in order to obtain an understanding of the category and proposed testing.

Dithiophosphate Alkyl Esters Category. Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program," in which use of chemical categories is encouraged, the following nine closely related chemicals constitute a chemical category:

- Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters – (CAS # 84605-28-7), referred to as "mixed 1,3-dimethylbutyl and iso-propyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters – (CAS # 68516-01-8), referred to as "mixed isobutyl and pentyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters – (CAS # 68784-30-5), referred to as "mixed sec-butyl and 1,3-dimethylbutyl derivative"
- Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters – (CAS # 113706-14-2), referred to as "mixed sec-butyl and isooctyl derivative"
- Phosphorodithioic acid, mixed 0,0-bis(2-ethylhexyl and iso-butyl) esters – (CAS # 68784-32-7), referred to as "mixed 2-ethylhexyl and isobutyl derivative"
- 2-Pentanol, 4-methyl-hydrogen phosphorodithioate – (CAS # 6028-47-3), referred to as "1,3-dimethylbutyl derivative"
- Phosphorodithioic acid, 0,0-bis(2-ethylhexyl) esters – (CAS# 5810-88-8), referred to as "2-ethylhexyl derivative"
- Phosphorodithioic acid, O,O-dioctyl ester, branched – (CAS# 68649-43-4), referred to as "branched isooctyl derivative"
- Phosphorodithioic acid, O,O-diisooctyl ester – (CAS# 26999-29-1), referred to as "isooctyl derivative"

An additional chemical that is not a part of the HPV Challenge Program but which is an analogue of these chemicals and fits into the Dithiophosphate alkyl esters category was used in the data review: Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters. The alkyl chains in this derivative (C4-C8) are within the range of the nine chemicals in the HPV category (C3-C8). This analogue has no CAS# because the substance was originally nominated as confidential to the U.S. TSCA Inventory and will be referred to as "mixed isobutyl, isooctyl and pentyl derivative".

Structural Similarity. A key factor supporting the classification of these chemicals as a category is their structural similarity. All substances in this category consist of a phosphorodithioic acid structure with alkyl ester substituent groups.

Similarity of Physicochemical Properties. The physicochemical properties of Dithiophosphate alkyl esters parallel their structural similarity. All members of this category are within a narrow molecular weight range (256 - 354 daltons) and are highly acidic. In addition, modeling data indicate they have similar melting and boiling points, low water solubility, low vapor pressure, and are lipophilic in nature.

Fate and Transport Characteristics. Members of this category are expected to be poorly biodegradable. Test data on the zinc dialkyldithiophosphate category will be used as surrogate data to adequately characterize this category for biodegradability. The members of the category are resistant to hydrolysis at room temperature because they lack readily hydrolyzable moieties. One member of this category was shown to be stable with respect to hydrolysis at room temperature. This makes hydrolysis modeling unnecessary and no further hydrolysis testing is proposed for this category. Photodegradation is not expected to cause significant physical degradation of Dithiophosphate alkyl esters. However, computer-modeled data will be developed to adequately characterize the potential atmospheric oxidation for members of this category. Although these substances are not expected to partition to water or air if released into the environment due to their low water solubility and low vapor pressure, computer-modeled environmental partitioning data will be calculated on the members of this category.

Toxicological Similarity. These chemicals are site-limited in their use and do not enter into commerce unreacted. Therefore, only a small amount of environmental and human health data exists on Dithiophosphate alkyl esters. Based on the extremely low risk of accidental or intentional environmental or human exposure, the nine substances in this category are of low environmental and human health concern. Data from additional work proposed in this test plan will further characterize the toxicity endpoints in the HPV Challenge Program for all members within this category.

> *Aquatic Toxicology.* No aquatic toxicity data exists for the Dithiophosphate alkyl esters. The structural similarity of the substances in this category is expected to create a predictable pattern in aquatic toxicity. Testing is proposed to adequately characterize this category for aquatic toxicity.
>
> *Mammalian Toxicology - Acute.* Data on acute mammalian toxicity were reviewed and, although minimal, the findings indicate that these chemicals, while corrosive to tissue, demonstrate a low concern for acute systemic toxicity. No additional acute mammalian toxicity testing is necessary for the following reasons: dithiophosphate alkyl esters are used as site limited intermediates; they are extremely corrosive to tissue; there is low risk of human exposure; and test animals will experience extreme pain and suffering with additional testing.
>
> *Mammalian Toxicology - Mutagenicity.* No data exist for bacterial reverse mutation, *in vitro* mutation assays in mammalian cells or *in vivo* chromosome aberration endpoints. Therefore, *in vitro* bacterial mutation and chromosome aberration testing will be conducted on the lowest molecular weight range of the component in the Dithiophosphate alkyl esters category (mixed 1,3-dimethylbutyl and iso-propyl derivative).

Mammalian Toxicology – Repeated-dose Systemic Toxicity and Reproduction and Developmental Toxicity. No data exist on the Dithiophosphate alkyl esters category for repeated-dose toxicity nor for reproduction and developmental toxicity. Acute dermal toxicity and irritation studies on experimental animals resulted in severe dermal irritation and corrosivity. There is minimal opportunity of human exposure to the chemicals in this category. Dithiophosphate alkyl esters exhibit extreme corrosive properties on skin. Therefore, additional repeated-dose and reproduction and developmental testing would only cause substantial distress and suffering in experimental animals and would add no additional insight into the risk of adverse health effects to Dithiophosphate alkyl esters from workplace exposure. The general public is not exposed to Dithiophosphate alkyl esters. Therefore, the HERTG concludes that no additional repeated-dose or reproduction and developmental testing will be performed on this category.

Exposure and Risk. Dithiophosphate alkyl esters are intended to undergo a further deliberate reaction to produce other HPV chemicals, generally those in the Zinc Dithiophosphate Category. Dithiophosphate alkyl esters are not transported or sold unneutralized. They are stored either *in situ* or on site. The risk to the environment for chemicals in the Dithiophosphate alkyl esters category is limited to accidental spills. Dithiophosphate alkyl ester tanks are diked and any spills are treated or removed for disposal and not allowed into the water systems. Dithiophosphate alkyl esters cause tissue burns and are used as site limited intermediates which are not drummed or loaded for transport. Therefore, exposure and risk of adverse health effects to humans and mammals is minimal due to the extreme care exercised in handling these chemicals.

Conclusion. Based on the data reviewed for this test plan, the individual physicochemical, environmental fate, and toxicological properties, the proposed Dithiophosphate alkyl esters category members are similar and/or follow a regular, predictable pattern based on chemical structure. Therefore, the EPA definition of a chemical category has been met, and the nine chemicals that constitute the Dithiophosphate alkyl esters category will be tested in accordance with the test plan summarized below.

Test Plan. The test plan for the Dithiophosphate alkyl esters category includes the following tests and computer modeling:

- Water solubility – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Photodegradation (atmospheric oxidation) modeling – Data will be developed using the AOP model in EPIWIN (1999). [EPIWIN. (1999). Estimation Program Interface for Windows, version 3.04. Syracuse Research Corporation, Syracuse, NY, USA.]
- Fugacity modeling – Environmental partitioning will be developed using a Mackay Level I (1998) equilibrium partitioning model. [Mackay, D. (1998). Level I Fugacity-Based Environmental Equilibrium Partitioning Model, Version 2.1 (16-bit). Environmental Modeling Centre, Trent University, Ontario, Canada.] and provided in robust summaries.
- Acute fish toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.
- Acute invertebrate toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.

- Alga toxicity – Testing will be conducted on the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS# 84605-28-7. Results will be bridged to other members of the category.
- Mutagenicity – Bacterial mutation and *in vitro* chromosome aberration studies will be conducted on mixed 1,3-dimethylbutyl and iso-propyl derivative (CAS# 84605-28-7). Results will be bridged to other members of the category.

As this test plan was developed, careful consideration was given to the number of animals that would be required for tests included in the proposed plan and conditions to which the animals might be exposed. In consideration of the concerns of some non-governmental organizations about animal welfare, the use of animals in this proposed test plan has been minimized.

TABLE OF CONTENTS

1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel's Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. This test plan follows up on that commitment.

Specifically, this test plan sets forth how the HERTG intends to address testing information for the following nine substances (structures are representative in Table 2):

- Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters – (CAS # 84605-28-7), referred to as "mixed 1,3-dimethylbutyl and iso-propyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters – (CAS # 68516-01-8), referred to as "mixed isobutyl and pentyl derivative"
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters – (CAS # 68784-30-5), referred to as "mixed sec-butyl and 1,3-dimethylbutyl derivative"
- Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters – (CAS # 113706-14-2), referred to as "mixed sec-butyl and isooctyl derivative"
- Phosphorodithioic acid, mixed 0,0-bis(2-ethylhexyl and iso-butyl) esters – (CAS # 68784-32-7), referred to as "mixed 2-ethyl hexyl and isobutyl derivative"
- 2-Pentanol, 4-methyl-hydrogen phosphorodithioate – (CAS # 6028-47-3), referred to as "1,3-dimethylbutyl derivative"
- Phosphorodithioic acid, 0,0-bis(2-ethylhexyl) esters – (CAS# 5810-88-8), referred to as "2-ethylhexyl derivative"
- Phosphorodithioic acid, O,O-dioctyl ester, branched – (CAS# 68649-43-4), referred to as "branched isooctyl derivative"
- Phosphorodithioic acid, O,O-diisooctyl ester – (CAS# 26999-29-1), referred to as "isooctyl derivative"

An additional chemical (Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters) was used in the data review. This chemical is not a part of the HPV Challenge Program but is an analogue of these chemicals and fits into the Dithiophosphate alkyl esters category. The alkyl chain in this derivative (C4-C8) is within the range of the nine chemicals in the HPV category (C3-C8). This analogue has no CAS# and will be referred to as "mixed C3-C8 Dithiophosphate Ester analogue derivative".

An analysis of the chemical structure of these chemicals supports the designation of the Dithiophosphate alkyl esters as a "chemical category" as provided in the EPA guidance document entitled, "Development of Chemical Categories in the HPV Challenge Program". This document provides the basis for that determination, indicates the findings of the data review process, and sets forth a proposed test plan to satisfy parts of the required test battery for endpoints without data that would be considered adequate under the program.

EPA guidance on the HPV Challenge Program indicates that the primary purpose of the program is to encourage "the chemical industry . . . to voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list." (EPA, "Development of Chemical Categories in the HPV Challenge Program," p. 1) At the same time, EPA recognizes that the "large number of chemicals to be tested [about 2800 HPV chemicals] makes it important to reduce the number of tests to be conducted, *where this is scientifically justifiable.*" (*Id.*, p. 1) [emphasis added].

> One approach is to test closely related chemicals as a group, or category, rather than test them as individual chemicals. In the category approach, *not every chemical needs to be tested for every SIDS endpoint.* However, *the test data finally compiled* for the category must prove adequate to support a screening level hazard-assessment of the category and its members. That is, the *final data set* must allow one to estimate the hazard for the untested endpoints, *ideally* by interpolation between and among the category members. In certain cases, where toxicity is low and no upward trend is expected, extrapolation to the higher category members may be acceptable. (*Id.*, p. 1) [emphasis added].

EPA guidance goes on to state, "The use of categories is encouraged in the Challenge Program and will have a number of benefits." (*Id.,* p. 1) Among the benefits identified in the guidance for the use of categories are "a reduction in testing will result in fewer animals used to test a category of chemicals as opposed to doing each test on each individual chemical," and "there will be . . . economic savings since less testing may be needed for chemicals considered as a category." (*Id.*, p. 1) That guidance also states that categories "accomplish the goal of the Challenge Program – to obtain screening level hazard information – through the strategic application of testing to the category." (*Id*, p. 2)

A similar intent "to reduce the number of tests to be conducted, *where this is scientifically justifiable*" was articulated by the Agency in its draft guidance document titled, "The Use of Structure Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program." [emphasis added].

The EPA "Chemical Categories" guidance sets forth a definition of what constitutes a "chemical category, for the purposes of the Challenge Program". Specifically, that definition states that a chemical category under the HPV Challenge Program "is a group of chemicals whose physicochemical and toxicological properties *are likely to* be similar *or* follow a regular pattern as a result of structural similarity." (*Op. Cit*., p. 2) [emphasis added].

According to the guidance, it is important that the "structural similarities [among members of the group] *may* create a predictable pattern *in any* or all of the following parameters: physicochemical properties, environmental fate and effects, and human health effects." (Id., p. 2) [emphasis added]. Thus, it is not necessary for the chemicals in a category to be similar in all respects. Nor must there be conclusive proof that the chemicals in the postulated category will behave identically across all relevant parameters. All that is required for an acceptable category under the HPV Challenge Program is that there be a *likelihood* of similarity of physicochemical and toxicological properties or a *likelihood* that the chemicals will in some pertinent respect follow a regular pattern as a result of their structural similarity.

In identifying the Dithiophosphate Ester category, the six-step process set out in the EPA guidance on category development was followed. As the information below indicates, the Dithiophosphate Ester chemicals clearly satisfy the standards established in that guidance for use of a chemical category:

Step 1: group structurally similar chemicals into a putative category

Step 2: gather relevant published and unpublished literature for each member of the category

Step 3: evaluate the compiled data for adequacy in accordance with the EPA guidance documentation

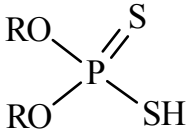
Step 4: construct matrices of SIDS endpoints versus category members arranged so as to indicate the structural progression of the category (in this case, by increasing molecular)

Step 5: evaluate the data to determine whether there is a correlation between category members for each SIDS endpoint

Step 6: make available to EPA, and to the public for review, this test plan including the foregoing category definition and rationale and the following data assessment with the proposed testing scheme for the Dithiophosphate alkyl esters.

2.0 DESCRIPTION

Dithiophosphate alkyl esters consist of a phosphorodithioic acid structure with alkyl ester substituent groups. The alkyl groups are saturated hydrocarbon chains that vary in length and extent of branching. An idealized structure is below:



The chemical names and CAS numbers for the members of the Dithiophosphate Ester category and analogue chemical are presented in Table 1 and the chemical structures in Table 2. These substances are prepared by reacting phosphorous pentasulfide with one or more primary or secondary alcohols to form the phosphorodithioic acid ester. Residual phosphorus pentasulfide is removed and stored as a closed system intermediate. These esters are not transported to other sites but are converted to the commercial zinc dialkydithiophosphates in a subsequent in-line step at the same manufacturing site.

The only structural variable that influences the molecular weight of the category members and consequently their bioavailability and toxicity is the length of the alkyl side chain, which may vary

from C3 to C8. The length and extent of branching of the alkyl side chain also affects the water solubility of these substances.

2.1 PHYSICOCHEMICAL PROPERTIES

Selected physicochemical properties of the members of the Dithiophosphate alkyl esters category are presented in Table 3. They are all amber colored viscous liquids at ambient temperature. The physicochemical properties of these substances, which are described below, are very similar, as would be expected based upon the similarity in their chemical structures. All members of this category are within a narrow molecular weight range (256 - 354 daltons) and are highly acidic. In addition, based on modeling data, they have similar melting and boiling points, low water solubility, low vapor pressure, and are lipophilic in nature. These properties provide support to the justification of this group of chemicals as a category within the HPV Challenge Program.

2.1.1 Molecular Weight and Alkyl Side Chain Length

The members of the category range in molecular weight from 256 to 354 daltons (Table 3).

2.1.2 PH

Dithiophosphate alkyl esters are strong acids. This acidity makes the members of this category corrosive.

2.1.3 Boiling Point

The Dithiophosphate alkyl esters differ only in the alkyl chain(s) present in the molecule. Therefore, the boiling points generally follow a pattern based upon their molecular weight and the extent of branching of the alkyl side chain. Modeling data indicates that the boiling point of these substances could range from 289 to 385^{o}C (Table 3).

2.1.4 Vapor Pressure

Modeling data indicates that the vapor pressure of these substances range from 3.46 x 10^{-3} to 1.9 x 10^{-5} mm Hg at 25^{o}C and generally follow a pattern based upon their molecular weight and the extent of branching of the alkyl side chain (Table 3).

2.1.5 Water Solubility

Modeling data indicates that these substances have low water solubility and that the log of the octanol-water partition coefficient (log $K_{o/w}$) of these substances range from 4.48 to 7.99 (Table 3). The low water solubility is consistent with the high lipophilic nature of these substances. The category member containing the shortest alkyl chain, mixed 1,3-dimethylbyutyl and isopropyl derivative (CAS# 84605-28-7) will be tested for water solubility.

3.0 QUALITATIVE EXPOSURE ASSESMENT OF DITHIOPHOSPHATE ALKYL ESTERS

Dithiophosphate alkyl esters are closed system intermediates. They are used by the member companies of the HERTG to produce components for lubricating oils by subsequent neutralization to form metal salts such as Zinc dialkyldithiophosphates. In all manufacturing sites in the United States, these materials are neutralized in the reaction vessel in which they are produced or stored in on-site facilities until neutralized. They are not transported to other manufacturing sites by members of the HERTG. Since the neutralization reactions that are used to produce the lubricating oil components use an excess of metal oxide or hydroxice, dithiophosphate alkyl esters are not present as in any end products at analytically detectable concentrations. Therefore, under prescribed conditions of use, the potential for exposure to the environment or to humans is extremely low.

4.0 EVALUATION OF AVAILABLE PUBLIC AND COMPANY DATA

4.1 Environmental Fate Data

4.1.1 Physicochemical Properties Relevant to Environmental Fate

In order to understand the environmental fate of a substance, one must understand how that substance can potentially partition among environmental compartments (i.e., air, soil, sediment, suspended sediment, water, and biota). The physicochemical properties of a substance influence the way in which a substance will degrade. The important environmental degradation pathways include biodegradation, hydrolysis, and photodegradation. Biodegradation is a measure of the potential of a compound to be degraded by microorganisms. Hydrolysis is a reaction in which a water molecule or hydroxide ion substitutes for another atom or group of atoms present in an organic molecule. Photodegradation is the degradation of a chemical compound as a result of absorption of solar radiation.

The physicochemical properties of the parent substance will influence the way in which these substances may partition among environmental compartments. Substances characterized by a low vapor pressure do not partition into air to any great extent. Similarly, substances that are characterized by low water solubility do not partition extensively into water. Substances that do not partition into air and water to any great extent tend to partition into soil and sediments.

4.1.2 Biodegradability

4.1.2.1 Test Methodologies

Chemical biodegradation involves a series of microbially-mediated reactions that may require many kinds of microorganisms acting together to degrade the parent substance. There are several standard test methods, which measure primary degradation (i.e., loss of parent chemical) or ultimate degradation (i.e., complete utilization of the substance to produce carbon dioxide, water, mineral salts, and microbial biomass). Primary degradation can be determined analytically by measuring dissolved organic carbon (DOC) for water-soluble chemicals, infrared absorbance, or by a chemical-specific detection method. Ultimate degradation (also called mineralization) can be determined by measuring oxygen consumption or carbon dioxide evolution relative to the theoretical levels that can be achieved based on an elemental analysis of the chemical under investigation.

4.1.2.2 Summary of Available Data

There are no current data available on the biodegradation of Dithiophosphate alkyl esters.

4.1.2.3 Data Assessment and Test Plan for Biodegradability

While no data exist on the biodegradation of Dithiophosphate alkyl esters, adequate biodegradation data exist for two of twelve substances in the zinc dialkyldithiophosphate category including the lowest molecular weight (CAS# 84605-29-8) and the highest molecular weight (CAS# 54261-67-5) members. These data are similar and indicate a narrow range of biodegradability irrespective of molecular weight and alkyl chain type. The hydrocarbon portion of these compounds that is susceptible to biodegradation is present in both the zinc dialkyldithiophosphates and the dithiophosphate alkyl esters. Therefore, it is expected that the dithiophosphate alkyl esters will behave similarly.
This makes biodegradability testing unnecessary and no further biodegradation testing is proposed for this category. Data from the zinc dialkyldithiophosphate category will be bridged to the members of the dithiophosphate alkyl esters category.

4.1.3 Hydrolysis

4.1.3.1 Test Methodologies

The potential for a substance to hydrolyze in water is assessed as a function of pH (OECD Guideline 111, *Hydrolysis as a Function of pH*[1]). When an organic molecule undergoes hydrolysis, a nucleophile (water or hydroxide ion) attacks an electrophile and displaces a leaving group (e.g., halogen, phenoxide).[2] Potentially

[1] Organization for Economic Cooperation and Development (OECD) (1993) OECD Guidelines for Testing of Chemicals. OECD. Paris, France.

[2] W. Lyman et al. (1990) *Handbook of Chemical Estimation Methods*. Chapter 8.

hydrolyzable groups include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters[4]. The lack of a suitable leaving group renders compounds resistant to hydrolysis.

4.1.3.2 Summary of Available Data

Hydrolytic evaluations on the 2-ethylhexyl derivative (CAS# 5810-88-8) member of the Dithiophosphate alkyl esters category have been performed at room temperature and at 80 degrees C. At room temperature, hydrolysis does not readily occur. When heated to 80 degrees C, hydrolytic degradation results in the formation of the phosphorothioic acid ester and hydrogen sulfide. Continued heating at high temperatures results in the formation of the mono-ester and eventually, phosphorothioic acid itself.

4.1.3.3 Data Assessment and Test Plan for Hydrolysis

The members of the category are resistant to hydrolysis at room temperature because they lack readily hydrolyzable moieties. This makes hydrolysis modeling unnecessary and no further hydrolysis testing is proposed for this category. Data from the 2-ethylhexyl derivative (CAS# 5810-88-8) will be bridged to the other members of the category.

4.1.4 Photodegradation

4.1.4.1 Test Methodologies

A prerequisite of photodegradation is the ability of one or more bonds of a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.

The Atmospheric Oxidation Potential (AOP) of a substance can be characterized using the modeling program AOPWIN. This computer simulation is recommended in the Agency's recently released structure activity review (SAR) guidance for HPV chemicals.

4.1.4.2 Summary of Available Data

There are no published or unpublished photodegradation studies for members of the Dithiophosphate alkyl esters category.

An initial review of the members of the Dithiophosphate alkyl esters category suggests that category members do not contain bonds that have a high potential to absorb UV light above 290 nm. These substances have low vapor pressure, which indicates that they have a low potential to partition into the air to a significant extent where they would be subject to indirect photodegradation.

4.1.4.3 Data Assessment and Test Plan for Photodegradation

HPV Challenge Program guidance suggests that photodegradation testing be performed on each member of a category or adequate data used to bridge from selected category members with data to the remaining members that have not been tested. The potential for category members to undergo direct photodegradation will be evaluated, also the AOP of selected category members will be characterized using the modeling program AOPWIN (Table 4). The AOP data for representative structures of the category will be evaluated to estimate (1) rate constants for the atmospheric, gas phase reaction as mediated by photochemically produced hydroxyl radicals and (2) atmospheric half-lives based on hydroxyl radical attack.

4.1.5 Fugacity Modeling

4.1.5.1 Modeling Methodologies

Fugacity-based multimedia fate modeling compares the relative distribution of chemicals among environmental compartments. A widely used model for this approach is the EQC model[3].

There are multiple levels of the EQC model. In the document, "Determining the Adequacy of Existing Data", EPA states that it accepts Level I fugacity modeling to estimate transport/distribution values. The Agency states that Level III model data are considered "more realistic and useful for estimating a chemical's fate in the environment on a regional basis". The EQC Level I model utilizes input of basic chemical properties, including molecular weight, vapor pressure, and water solubility to calculate percent distribution within a standardized environment. EQC Level III uses these parameters to evaluate chemical distribution based on discharge rates into air, water, and soil, as well as degradation rates in air, water, soil, and sediment.

4.1.5.2 Summary of Available Data

There are no published or unpublished fugacity-based multimedia fate modeling data for members of the Dithiophosphate alkyl esters category. Modeling data indicate that all of the members of this category have low vapor pressure and low water solubility signifying that they will not tend to partition into the air or water to any great extent. Modeling data indicates that these substances are hydrophobic in nature, which suggests that any which reaches the water compartment will be immobilized through binding to the organic component of soils and sediments.

4.1.5.3 Test Plan for Fugacity

HPV Challenge Program guidance suggests that fugacity modeling be performed on each member of a category or adequate data used to bridge from selected category members with data to the remaining members that have not been tested. The relative distribution of substances within this category among environmental compartments will be evaluated using the Level I model. Data developed using a

[3] Equilibrium Criterion Model- Environmental Modeling Centre as developed by D. Mackay.

Level I model can then be used for simple comparative purposes across several substances. EQC Level III will not be used for this evaluation because appropriate emission levels are as yet unknown. Because of the physical nature of the substances in this category, a Level I data set will be as equally robust as a Level III data set and can then be used to assess the potential partitioning behavior of Dithiophosphate alkyl esters category members in the environment.

Input data to run the EQC Level I model may require an additional computer model to estimate selected physical/chemical properties from a structure. The model used for this purpose will be EPIWIN, version 3.04[4], which was developed by the Syracuse Research Corporation. EPIWIN includes algorithms for estimating all physical and chemical properties needed for the EQC model.

4.2. ECOTOXICOLOGY DATA

4.2.1 Aquatic Ecotoxicity Testing

4.2.1.1 Test Methodologies

Acute aquatic ecotoxicity tests are usually conducted with three species that represent three trophic levels in the aquatic environment: fish, invertebrates, and algae. The fish acute toxicity test (OECD Guideline 203, *Fish, Acute Toxicity Test*) establishes the lethality of a substance to a fish during a 96-hour exposure period. The acute invertebrate test (OECD Guideline 202, *Daphnia sp., Acute Immobilization Test and Reproduction Test*) establishes the lethality of a substance to an invertebrate, typically a daphnid (*Daphnia magna*), during a 48-hour exposure period. The alga growth inhibition test (OECD Guideline 201, *Alga, Growth Inhibition Test*) establishes the potential of a substance to inhibit alga growth, typically using the freshwater unicellular green algae, *Pseudokirchneriella subcapitata* (formerly called *Selenastrum capricornutum*), during a 96-hour exposure period.

Three test methodologies are commonly used to conduct aquatic toxicity tests; i.e., flow-through, static, and static renewal tests.

In *flow-through tests*, organisms are continually exposed to fresh chemical concentrations in each treatment level in the incoming water resulting in greater assurance that the exposure levels and water quality will remain constant throughout the test. Although flow-through testing is the preferred method, it is only applicable for chemicals that have adequate water solubility for testing.

In *static tests*, organisms are exposed in the test medium that is not replaced for the duration of the study. There is less assurance that the test concentrations will remain

[4] EPIWIN. 1999. Estimation Program Interface for Windows, version 3.04. SyracuseResearchCorporation, Syracuse, NY, USA.

constant because test material can be adsorbed onto test chambers, degraded, volatilized, or otherwise changed during the test. Nevertheless, due to limitations of other test systems for non-volatile materials, the static test has been widely used, especially for testing organisms such as algae and *Daphnia*.

The *static-renewal test* is similar to a static test because it is conducted in still water, but the test solutions and control water are renewed periodically, usually every 24 hours. Daily test solution renewal provides a greater likelihood that the exposure concentrations will remain stable throughout the test. This is the preferred method for conducting aquatic toxicity tests for compounds such as the Dithiophosphate Ester on fish. Daily renewals cannot be done in the algae test, and usually not in *Daphnia* tests, because the process of separation and replenishment would cause a discontinuity in the alga growth rate and it can stress, coat, or entrap *Daphnia* in any surface film during renewals. OECD considers the use of static test for *Daphnia* and algae, and the use of static renewal test for fish to be appropriate for testing poorly soluble chemicals like the Dithiophosphate Ester provided that test solutions are prepared using water accommodated fraction or water soluble fraction methods.[7]

4.2.1.2 Test Solution Preparation

Dithiophosphate alkyl esters have a low degree of water solubility and it is not possible to prepare exposure solutions for aquatic toxicity testing by direct addition of measured quantities of test material to water. Two methods[6] are used to prepare solutions of poorly water-soluble materials for aquatic toxicity testing:

- *Water accommodated fraction* (WAF) – This is a method in which the test solution contains only that fraction of the test material (organic phase) which is retained in the aqueous phase after a period of stirring long enough to reach equilibrium, followed by a sufficient time (1-4 hours) for phase separation. The WAF (aqueous phase) will contain soluble components of the test material at levels that will be dependent on the test material loading (the amount of material added to the aqueous medium). The resulting WAF is used in the aquatic toxicity test. Ideally, a WAF consists of a water-soluble extract of test material, but it can also include a stable micro-emulsion or contain small amounts of suspended matter.

- *Water soluble fraction* (WSF) – This is a method in which a WAF is either filtered, centrifuged, or allowed to settle for a greater length of time (24 hours) than with the WAF method to remove suspended matter from the aqueous phase before being used in the aquatic toxicity test.

[5] Organization for Economic Cooperation and Development (OECD) (2000). Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. OECD Environmental Health and Safety Publications, Series on Testing and Assessment No.23, Paris, France.

[6] American Society for Testing and Materials (1998) D6081-98, Standard Practice for Aquatic Toxicity Testing of Lubricants: Sample Preparation and Results Interpretation.

4.2.2 Aquatic Toxicity of the Dithiophosphate alkyl esters

In general, the toxicity of a substance to an organism is limited by mechanisms of uptake and movement to target organs. Characteristics such as smaller molecular size and a lesser degree of ionization increase the ability of a substance to passively cross biological membranes. However, the soluble fraction of a compound in water represents the chemical fraction responsible for toxicity to aquatic organisms. Therefore, aquatic toxicity can be limited by the water solubility of a substance.

Data and preliminary modeling information indicates that all members of the Dithiophosphate alkyl esters category have low water solubility. The low water solubility suggests that the acute aquatic toxicity of these substances should be low due to limited bioavailability to aquatic organisms. However, the length of the alkyl side chains on these substances will influence their relative water solubility, and, hence, their relative toxicity. Modeling data indicate that the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS # 84605-28-7) is predicted to be the most water-soluble member of the category and therefore, it is the member most likely to demonstrate potential aquatic toxicity.

4.2.2.1 Summary of Available Data

4.2.2.1.1 Fish Acute Toxicity

There are no published or unpublished fish acute toxicity data for members of the Dithiophosphate alkyl esters category.

4.2.2.1.2 Invertebrate Acute Toxicity

There are no published or unpublished invertebrate acute toxicity data for members of the Dithiophosphate alkyl esters category.

4.2.2.1.3 Alga Toxicity

There are no published or unpublished alga acute toxicity data for members of the Dithiophosphate alkyl esters category.

4.2.2.2 Data Assessment and Test Plan for Acute Aquatic Ecotoxicity

Each of the ecotoxicity endpoints must be tested within a narrow pH range (6.5 to 8.5), consistent with maintaining the viability of the test organisms. OECD Guidelines allow for the adjustment of pH with simple acid or alkali (or other suitable buffer). If needed, adjustment of the pH of the media will be made.

Modeling data predict that the mixed 1,3-dimethylbutyl and isopropyl derivative (CAS # 84605-28-7) is the most water-soluble and insoluble member of the category. Therefore, this category member is the most likely to represent the lower bound of aquatic toxicity. Acute testing in fish, daphnia, and algae will be conducted on this substance and the results will be bridged to other members of the category.

4.3 MAMMALIAN TOXICOLOGY DATA

4.3.1 Physicochemical Properties Relevant to Mammalian Toxicity

Physicochemical properties of chemicals are useful for predicting the routes by which exposure may occur, and in some cases, the mechanism and extent of toxicological responses. The physicochemical properties of the Dithiophosphate alkyl esters are presented in Table 3. The structural and physical properties such as comparatively high molecular weight, the presence of long-chain alkyl moieties and poor water solubility is expected to impede the rate and extent of skin absorption of Dithiophosphate -the most likely route of human exposure. Additionally, the Dithiophosphate alkyl esters are high viscosity liquied compounds with high boiling points and low vapor pressure. As a result, these substances have a low propensity to form vapors or aerosols, and thus, unintentional exposure via inhalation is unlikely.

4.3.2 Acute Mammalian Toxicity of the Dithiophosphate alkyl esters

4.3.2.1 Acute Toxicity Test Methodology

Acute toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. Potential routes of exposure for acute toxicity assays include oral, dermal, and inhalation. Oral toxicity assays are conducted by administering test material to fasted animals (typically rats or mice) in a single gavage dose. Acute dermal toxicity tests are conducted by administering test material to the shaved skin on the back of the test animal (typically rats or rabbits) and allowing the test material to stay in contact with the skin application site for a specific duration (usually 24 hours). Acute inhalation toxicity assays are conducted by exposing test animals (typically rats) in a controlled atmosphere to a fixed air concentration of the test substance for a specific duration (typically 4 hours). The test material is either generated as a vapor or intentionally aerosolized into respirable particles, then metered into the exposure air at the desired concentration. Preferably, inhalation toxicity studies are conducted using either nose-only or head-only exposure to minimize potential confounding effects resulting from whole-body exposure. Whole body exposure may lead to over-prediction of inhalation toxicity hazard by increasing the body-burden of the test material through skin absorption or ingestion of test material as a consequence of grooming both during and after the inhalation exposure period.

Historically, lethality is a primary end-point of concern in acute toxicity studies, and the traditional index of oral and dermal potency is the median lethal dose that causes mortality in 50 percent of the test animals (LD_{50}). In acute inhalation studies, the traditional measurement of potency is the median lethal concentration of the test material in air that causes mortality in 50 percent of the test animals (LC_{50}). In addition to lethality, acute toxicity studies also provide insights regarding potential systemic toxicity through careful observation and recording of clinical signs and

symptoms of toxicity as well as through detailed examination of tissues and organ systems.

Typically, acute oral and dermal toxicity studies are conducted using a limit dose of 5,000 and 2,000 mg/kg body weight, respectively, and acute inhalation toxicity studies are conducted using a limit dose of 5 mg/L for 4 hours (according to OECD and EPA testing guidelines). Prior to 1990, some acute dermal toxicity studies may have used a limit dose of 5,000 mg/kg. Recently, harmonized EPA testing guidelines (August 1998) have set the limit dose for both oral and dermal acute toxicity studies at 2,000 mg/kg body weight, while the recommended limit concentration for acute inhalation studies has been set at 2 mg/L for 4 hours. The limit dose test method minimizes the number of animals tested by exposing a single group of animals to a large dose (the limit dose) of the test substance. A test substance that shows little or no effects at the limit dose is considered essentially nontoxic, and no further testing is needed. If compound-related mortality is observed at the limit dose, then further testing may be necessary.

4.3.2.2 Summary of Available Data

4.3.2.2.1 Acute Oral Toxicity

There is a literature citation for an oral LD_{50}=2,140 ml/kg[7] for the 2-ethylhexyl derivative.

4.3.2.2.2 Acute Dermal Toxicity

There is a literature citation for a dermal LD50=1,250 ml/kg[8] for the 2-ethylhexyl derivative. Additionally, an acute dermal toxicity study is available analogue known as “mixed C3-C8 Dithiophosphate Ester analogue derivative”. This was a limit test conducted under a protocol similar to the OECD Guideline 402 with the exception that abraded skin was treated. Although no deaths occurred at 2,000 mg/kg, animals demonstrated necrosis, edema and ulceration throughout the study observation period. This was demonstrates the corrosivity of these chemicals.

4.3.2.2.3 Acute Inhalation Toxicity

There is one acute inhalation toxicity study on a Dithiophosphate alkyl esters chemical. The relevance of these data is questionable since the mixed C3-C8 Dithiophosphate Ester analogue derivative Dithiophosphate alkyl esters was preheated to 100^{o} C to obtain the maximum attainable nominal concentration of 0.198 mg/L. This vapor was administered to 5 male and 5 female Sprague-Dawley rats for 4 hrs. The atmosphere also contained 74.2 ppm of H2S. No rats died during exposure. Lacrimation was observed during exposure, salivation and redness/discoloration around the nose and mouth were noticed after exposure. All rats returned to normal within 7 days. One female had gray lungs

[7] American Industrial Hygiene Association Journal. V.25, pg. 95. 1962
[8] Ibid

at necropsy; all others were within normal limits. The LC_{50} for as C3-C8 Dithiophosphate Ester analogue derivative was greater than 0.198 mg/L.

4.3.2.5 Eye and Skin Irritation

A primary skin irritation study in rabbits was conducted on the C3-C8 Dithiophosphate Ester analogue derivative. The chemical was applied to 2 abraded and 2 intact sites on the shaved backs of 4 male and 2 female New Zealand albino rabbits at the rate of 0.5 ml to each site. Each site was covered with a 2.5 cm^2 adhesive dressing. Coverings were removed after 24 hours. Test sites were Draize scored at 1, 3, 7, 14, and 21 days after application. Severe damage to the skin was seen in all animals. Edema, erythema and/or eschar formation was observed at the test sites of all rabbits at all scoring intervals. Necrosis was evident 1, 3, and 7 days following chemical application. The primary dermal irritation score was 8.0/8.0.

An eye irritation study in rabbits was conducted on C3-C8 Dithiophosphate Ester analogue derivative. 0.1 ml of neat chemical was instilled in the right eyes of 3 male and 3 female New Zealand albino rabbits. The eyes were Draize scored for irritation at 1, 2, 3, 4, 7, 14, and 21 days. The maximum irritation score of 78.5/110.0 was obtained 1 day after installation of the chemical. All rabbits exhibited eye irritation and recovery was not complete in any rabbit by day 21. One male rabbit was euthanized at day 14 due to the severity of the ocular reaction.

These studies demonstrated the corrosive nature of Dithiophosphate alkyl esters.

4.3.2.3 Data Assessment and Test Plan for Acute Mammalian Toxicity

Acute mammalian toxicity tests were available on a lower molecular weight analogue for this category. The molecular weight range of this category is fairly narrow (C3-C8) and the alkyl groups similar. Therefore, the acute toxicity is not expected to vary greatly. Due to the corrosivity of these chemicals, as seen in the eye and skin irritation studies, to spare animals from unnecessary pain and suffering, no additional acute mammalian toxicity testing will be conducted on the Dithiophosphate alkyl esters category constituents. Bridging will be used to all Dithiophosphate alkyl esters based on the C3-C8 Dithiophosphate Ester analogue derivative data.

4.3.3 Mutagenicity of the Dithiophosphate alkyl esters category

4.3.3.1 Mutagenicity Test Methodology

Genetic toxicology is concerned with the effects of substances on genetic material (i.e., DNA and chromosomes). Within genetic material, the gene is the simplest functional unit composed of DNA. Mutations are generally non-lethal, heritable changes to genes that may arise spontaneously or because of xenobiotic exposure. Genetic mutations are commonly measured in bacterial and mammalian cells. The simplest test systems measure the occurrence of a base-pair substitution mutation in

which a single nucleotide is changed followed by a subsequent change in the complementary nucleotide on the other DNA strand. Frame shift mutations occur following the deletion or insertion of one or more nucleotides, which then changes the "reading frame" for the remainder of the gene or multiple genes. Genetic testing for these types of point mutations is generally accomplished by *in vitro* cellular assays for forward or reverse mutations. A forward mutation occurs when there is a detectable change in native DNA whereas a reverse mutation occurs when a mutated cell returns to its initial phenotype. Both base-pair substitutions and frame shift mutations are routinely measured in bacterial cells by measuring the ability of a cell to acquire the capability to grow in an environment missing an essential amino acid. In these tests, a large number of cells are examined to demonstrate a significant increase in the frequencies of mutations that occur over the frequency of spontaneous mutations.

Chromosomal aberrations are large scale numerical or structural alterations in eukaryotic chromosomes including deletions (visualized as breaks), translocations (exchanges), non-disjunction (aneuploidy), and mitotic recombination. Chromosomal breakage is the classical end point in chromosomal aberration assays. Substances that induce structural changes in chromosomes, especially chromosome breaks, are referred to as "clastogens." To visualize chromosomes and chromosomal aberrations following *in vitro* or *in vivo* treatment with a substance, cells are arrested in metaphase, treated to swell the chromosomes, fixed, transferred to slides and stained. The first metaphase following treatment is the time at which the greatest number of cells with damaged chromosomes may be observed. The most frequently used test systems investigate changes in mammalian cells (such as Chinese hamster ovary or lung cells; human or rat lymphocytes; or human, rat or mouse bone marrow cells) following either *in vitro* or *in vivo* exposure to the test substance. The micronucleus test is a common *in vivo* assay that measures the frequency of micronuclei formation (i.e., chromosomal fragments) in polychromatic erythrocytes.

4.3.3.2 Summary of Mutagenicity Data

4.3.3.2.1 Bacterial Gene Mutation Assay

There are no Bacterial Gene Mutation studies on Dithiophosphate alkyl esters.

4.3.3.2.2 Mammalian Gene Mutation Assay

There are no data Mammalian Gene Mutation studies on Dithiophosphate alkyl esters.

4.3.2.2.4 *In vivo* Chromosomal Aberration Assays

There are no *in vivo* chromosomal aberration studies on Dithiophosphate alkyl esters.

4.3.3.3 Data Assessment and Test Plan for Mutagenicity

Since there are no data on the mutagenicity of the Dithiophosphate alkyl esters category, we will conduct a bacterial gene mutation assay and an *in vitro*

chromosomal aberration assay on the mixed 1,3-dimethylbutyl and iso-propyl derivative. This is the lowest molecular weight components of this category which will represent the "worse case" genetic toxicity of the very similar chemicals in this category.

4.3.4 Repeated-dose Toxicity of the Dithiophosphate alkyl esters category

4.3.4.1 Repeated-dose Toxicity Test Methodology

Repeated-dose toxicity studies evaluate the systemic effects of repeated exposure to a chemical over a significant period of the life span of an animal (rats, rabbits, or mice). Chronic repeated-dose toxicity studies are concerned with potential adverse effects upon exposure over the greater part of an organism's life span (e.g., one to two years in rodents). Subchronic repeated-dose studies are also concerned with effects caused by exposure for an extended period, but not one that constitutes a significant portion of the expected life span. Subchronic studies are useful in identifying target organ(s), and they can be used in selecting dose levels for longer-term studies. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of at least 28 days or up to 90 days (i.e., 4 to 13 weeks). A recovery period of two to four weeks (generally included in most study designs) following completion of the dosing or exposure period provides information on whether or not the effects seen during the exposure period are reversible upon cessation of treatment. The dose levels evaluated in repeated-dose toxicity studies are notably lower than the relatively high limit doses used in acute toxicity studies. The NOAEL (no observed adverse effect level), usually expressed in mg/kg/day, defines the dose of test material that produces no significant toxicological effects. If the test material produces toxicity at the lowest dose tested (i.e., there is no defined NOAEL), the lowest dose that produced an adverse effect is defined as the LOAEL (lowest observed adverse effect level). While these studies are designed to assess systemic toxicity, the study protocol can be modified to incorporate evaluation of potential adverse reproduction and/or developmental effects.

Reproduction and developmental toxicity studies generate information on the effects of a test substance on male and female reproduction performance such as gonadal function, mating behavior, conception, and development of the conceptus, parturition, and post-partum development of the offspring. Various study designs exist, but they all involve exposure to both male and female test animals before mating. The rat is most often selected as the test species. The test substance is administered to males and females continuously at several graduated doses for at least two weeks prior to mating and until the animals are sacrificed. The males are treated for at least two more weeks. Male gonadal histopathology is carefully assessed at the end of the study. The females are treated through parturition and early lactation. The adult females and offspring are typically studied until termination on post-natal day 21, or sometimes earlier. In addition to providing data on fertility and reproduction, this study design provides information on potential developmental toxicity following prenatal and limited post-natal exposure to the

test substance. An NOAEL or LOAEL is also used to describe the results of these tests, with the exception that these values are derived from effects specific to reproduction or development.

The "toxicity to reproduction" requirement in the HPV Challenge Program can be met by conducting the *Reproduction/Developmental Toxicity Screening Test* (OECD Guideline 421) or by adding this screening test to a repeated-dose study (OECD Guideline 422, *Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*). The *One-Generation Reproduction Toxicity Study* (OECD Guideline 415) is a more comprehensive protocol for the study of the effect of a test material on reproduction and development that also meets the OECD SIDS and the HPV Challenge Program requirements.

4.3.4.2 Summary of Repeated-Dose Toxicity Data

4.3.4.2.1 Systemic Toxicity Tests

There are no systemic toxicity tests on Dithiophosphate alkyl esters.

4.3.4.2.2 Reproduction and Developmental Toxicity Tests

There are no reproduction and developmental toxicity tests on Dithiophosphate alkyl esters.

4.3.5 Data Assessment and Test Plan for Repeated-dose Toxicity

The exposure profile of Dithiophosphate alkyl esters offers assurance that there is minimal risk for repeated dose toxicity. Dithiophosphate alkyl esters are site limited, closed system intermediates. They are stored on-site and not transported to other locations. Therefore, the only realistic exposure scenario is during the manufacture of Dithiophosphate alkyl esters. Manufacture of Dithiophosphate alkyl esters is conducted in closed reaction vessels and transfers are performed in closed system pipes. The exposure potential to production workers is very low due to process, engineering and personal protection equipment controls. For concentrated component, the only practical type of exposure would be acute and only occur in the rare case of an accidental spill. The dermal route would be the principle route of exposure. Oral or inhalation exposure is expected to be rare.

Additionally, Dithiophosphate alkyl esters are corrosive. Therefore, the handling and storage conditions lead to a limited potential for long-term exposure. In this case, EPA and ICCA recognizes the need to tailor the HPV test plans to reflect the information needed to evaluate the hazards in case of an accident. Since exposures resulting from chemical accidents are likely to be of relatively short versus chronic duration, we will not conduct repeated-dose toxicity, developmental or reproduction/developmental toxicity testing. This is considered the appropriate level of testing for screening purposes.

In addition to the arguments outlined above, HERTG believes that additional testing of Dithiophosphate alkyl esters will cause unnecessary distress to experimental animals.

Previously conducted experimental studies demonstrate Dithiophosphate alkyl esters are corrosive to skin, eye and mucosal membranes. Animals used in the acute skin irritation studies exhibited severe local skin damage caused by administrations of Dithiophosphate alkyl esters. During the acute eye irritation study, one animal had to be sacrificed for humane reasons due to its extreme distress. Thus, the principal hazard of Dithiophosphate alkyl esters is their corrosive effects.

"EPA has committed to examining alternative test methods that reduce animals needed for testing, that reduce pain and suffering of test animals…".[9] HERTG shares EPA's commitment to reduce the number of animals needed for testing and to reduce pain and suffering of test animals to the extent that it is practical and scientifically justifiable. Based on a thoughtful scientific review and the limited potential for intentional or accidental human exposure, the sponsoring companies of HERTG would be unable to conduct additional mammalian toxicity testing on Dithiophosphate alkyl esters without imparting unnecessary distress and suffering to the experimental animal. We believe that by not conducting mammalian toxicity tests on chemicals known to be corrosive and that have limited risk of exposure to the environment and to humans, we are supporting the spirit of this commitment.

[9] Chemical Right to Know High Production Volume Challenge Program "**Fact Sheet on Animal Welfare"**.

Table 1. Members of the Dithiophosphate Ester Category
(In estimated lowest to highest molecular weight order)

CAS Number	Chemical Name	Simplified Chemical Name
84605-28-7	Phosphorodithioic acid, mixed O,O-bis (1,3-dimethylbutyl and iso-propyl) esters	mixed 1,3-dimethylbutyl and iso-propyl derivative
68516-01-8	Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters	mixed isobutyl and pentyl derivative
68784-30-5	Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3 dimethylbutyl) esters	mixed sec-butyl and 1,3-dimethylbutyl derivative
None Assigned (analogue)	Phosphorodithioic acid, mixed O,O-bis(iso-Bu and isooctyl and pentyl) esters	mixed isobutyl, isooctyl and pentyl derivative
113706-14-2	Phosphorodithioic acid mixed O,O-bis(sec-butyl and isooctyl) mixed esters	mixed sec-butyl and isooctyl derivative
68784-32-7	Phosphorodithioic acid, mixed 0,0-bis(2-ethylhexyl and iso-butyl) esters	mixed 2-ethyl hexyl and isobutyl derivative
6028-47-3	2-Pentanol, 4-methyl-hydrogen phosphorodithioate	1,3-dimethylbutyl derivative
5810-88-8	Phosphorodithioic acid, 0,0-bis(2-ethylhexyl) esters	2-ethylhexyl derivative
68649-43-4	Phosphorodithioic acid, O,O-dioctyl ester, branched	branched isooctyl derivative
26999-29-1	Phosphorodithioic acid, O,O-diisooctyl ester	isooctyl derivative

Table 2. Chemical Structures comprising the Dithiophosphate alkyl esters category

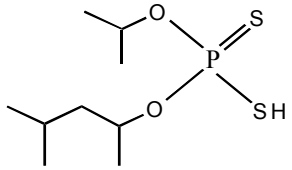
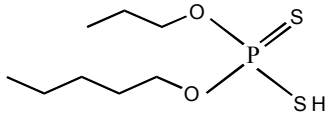
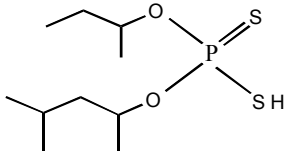
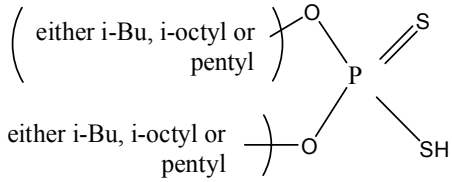
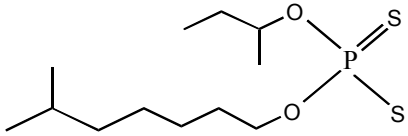
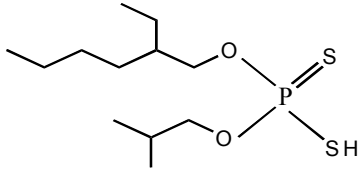
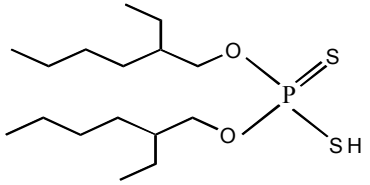
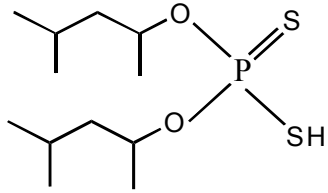
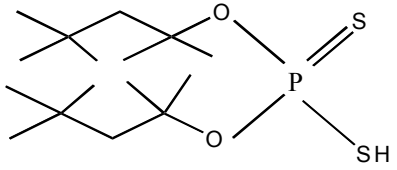
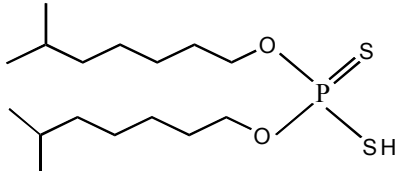
CAS Number	Structure	CAS Number	Structure
84605-28-7	 + other combinations	68516-01-8	 + other combinations
68784-30-5	 + other combinations	mixed isobutyl, isooctyl and pentyl derivative	
113706-14-2	 + other combinatio	68784-32-7	 + other combinations
6028-47-3		5810-88-8	
68649-43-4		26999-29-1	

Table 3. Physicochemical Properties of Dithiophosphate alkyl esters

CAS Number	Molecular Weight	MP[1] °C	BP[1] °C	Vapor Pressure mm Hg[1]	Water Solubility mg/L[1]	Log K_{ow}[1]
84605-28-7	256	-39	289	0.00346	3.277	4.48
68516-01-8	256	-18	307	0.00134	2.454	4.62
68784-30-5	270	-29	304	0.00157	1.04	4.97
mixed isobutyl, isooctyl and pentyl derivative	270	No data	No data	No data	No data	No data
113706-14-2	298	0	339	0.000246	0.08998	6.02
68784-32-7	298	0	339	0.000246	0.08998	6.02
6028-47-3	298	-19	323	0.00056	0.1201	5.88
5810-88-8	354	-13	385	1.9×10^{-5}	0.0008768	7.99
68649-43-4	354	16	353	0.000113	0.001573	7.69
26999-29-1	354	-13	385	1.9×10^{-5}	0.0008768	7.99

[1]Data derived from modeling

Table 4. Evaluation of Environmental Fate Information for Dithiophosphate alkyl esters

CAS Number	BIODEGRADABILITY Available Data & Proposed Testing	HYDROLYSIS Available Data & Proposed Testing	PHOTODEGRADATION Available Data & Proposed Testing
84605-28-7	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
68516-01-8	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
68784-30-5	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
mixed isobutyl, isooctyl and pentyl derivative	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
113706-14-2	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
68784-32-7	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
6028-47-3	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
5810-88-8	No testing needed Bridging[1]	Does not readily occur	Direct photodegradation evaluation AOPWIN Model Estimation
68649-43-4	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation
26999-29-1	No testing needed Bridging[1]	No testing needed Bridging	Direct photodegradation evaluation AOPWIN Model Estimation

[1]Bridging from zinc dialkyldithiophosphates category data.

Table 5. Evaluation of Aquatic Toxicology of Dithiophosphate alkyl esters

CAS Number	ACUTE TOXICITY TO FISH 96-hr LL_{50} (mg/L)[1]	ACUTE TOXICITY TO INVERTEBRATES 48-hr EL_{50} (mg/L)[1]	TOXICITY TO ALGAE 96-hr EL_{50} (mg/L)[1]
	Available Data & Proposed Testing	Available Data & Proposed Testing	Available Data & Proposed Testing
84605-28-7	Test	Test	Test
68516-01-8	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
68784-30-5	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
mixed isobutyl, isooctyl and penty derivative	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
113706-14-2	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
68784-32-7	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
6028-47-3	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
5810-88-8	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
68649-43-4	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging
26999-29-1	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging

Table 6. Evaluation of Acute Mammalian Toxicology of Dithiophosphate alkyl esters

CAS Number	ACUTE ORAL TOXICITY[1]	ACUTE DERMAL TOXICITY[1]	ACUTE INHALATION TOXICITY[2]	PRIMARY DERMAL IRRITATION	EYE IRRITATION
	Available Data & Proposed Testing	Available Data & Proposed Testing	Available Data & Proposed Testing	Available Data	Available Data
84605-28-7	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
68516-01-8	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
68784-30-5	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
mixed isobutyl, isooctyl and pentyl derivative	No testing needed Bridging	>2,000 mg/kg	>0.198 mg/L (nominal concentration)	Severe damage to the skin. Edema, erythema and/or eschar formation was observed at the test sites of all rabbits at all scoring intervals. Necrosis was evident on days 1, 3, and 7 following chemical application. The primary dermal irritation score was 8.0/8.0.	Maximum irritation score of 78.5/110.0 (day 1). All rabbits exhibited eye irritation and recovery was not complete in any rabbit by day 21. One rabbit euthanized at day 14 due to the severe ocular reaction.
113706-14-2	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
68784-32-7	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
6028-47-3	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
5810-88-8	2140 ml/kg[3]	1250 ml/kg[3]	No testing needed Bridging		
68649-43-4	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		
26999-29-1	No testing needed Bridging	No testing needed Bridging	No testing needed Bridging		

[1]Toxicity endpoints are expressed as median lethal dose (LD_{50}) for dermal toxicity**.**

[2]Toxicity of endpoint is expressed as median lethal concentration (LD_{50}) for inhalation toxicity

[3]Smyth, Henry F., Charles P. Carpenter, Carrol S. Weil, Urbano C. Pozzani, and Jean A. Striegel. "Range-Finding Toxicity Data: List VI." American Industrial Hygiene Association Journal 1962. 23:95.

Table 7. Evaluation of Mutagenicity of Dithiophosphate alkyl esters

CAS Number	GENE MUTATION ASSAY Available Data & Proposed Testing	CHROMOSOMAL ABERRATION ASSAY Available Data & Proposed Testing
84605-28-7	Test	Test
68516-01-8	No testing needed Bridging	No testing needed Bridging
68784-30-5	No testing needed Bridging	No testing needed Bridging
mixed isobutyl, isooctyl and pentyl derivative	No testing needed Bridging	No testing needed Bridging
113706-14-2	No testing needed Bridging	No testing needed Bridging
68784-32-7	No testing needed Bridging	No testing needed Bridging
6028-47-3	No testing needed Bridging	No testing needed Bridging
5810-88-8	No testing needed Bridging	No testing needed Bridging
68649-43-4	No testing needed Bridging	No testing needed Bridging
26999-29-1	No testing needed Bridging	No testing needed Bridging

Table 8. Evaluation of Evaluation of Repeated-dose Mammalian Toxicology of Dithiophosphate alkyl esters

CAS Number	REPEATED-DOSE TOXICITY	REPRODUCTIVE/DEVELOPMENTAL TOXICITY
	Available Data & Proposed Testing	Available Data & Proposed Testing
84605-28-7	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
68516-01-8	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
68784-30-5	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
mixed isobutyl, isooctyl and pentyl derivative	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
113706-14-2	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
68784-32-7	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
6028-47-3	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
5810-88-8	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
68649-43-4	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical
26999-29-1	No testing proposed due to corrosivity of chemical	No testing proposed due to corrosivity of chemical

CAS Number	Environmental Fate					Ecotoxicity			Human Health Effects				
	Physical Chem	Photodeg	Hydrolysis	Fugacity	Biodeg	Acute Fish Toxicity	Acute Invert Toxicity	Algal Toxicity	Acute Toxicity	Point Mutations	Chrom Effects	Sub-chronic	Repro/ Develop
84605-28-7	T	M	B	M	B	T	T	T	B	T	T	I	I
68516-01-8	A	M	B	M	B	B	B	B	B	B	B	I	I
68784-30-5	A	M	B	M	B	B	B	B	B	B	B	I	I
mixed isobutyl, isooctyl and pentyl derivative	A	M	B	M	B	B	B	B	A	B	B	I	I
113706-14-2	A	M	B	M	B	B	B	B	B	B	B	I	I
68784-32-7	A	M	B	M	B	B	B	B	B	B	B	I	I
6028-47-3	A	M	B	M	B	B	B	B	A	B	B	I	I
5810-88-8	A	M	A	M	B	B	B	B	B	B	B	I	I
68649-43-4	A	M	B	M	B	B	B	B	B	B	B	I	I
26999-29-1	A	M	B	M	B	B	B	B	B	B	B	I	I

A Adequate data available
M Computer modeling proposed
B Read across
D Technical discussion proposed
T Test
I Inappropriate due to corrosivity of chemical and risk and exposure analysis

Additional Studies not included in this Test Plan

None

Substance Group: **Group 4: Dithiophosphate Alkyl Esters**

Summary prepared by: **Petroleum Additives Panel**
Health & Environmental Research Task Group

Date of last update: **October 7, 2002**

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1.0 Mammalian

1.1 Acute Dermal Toxicity

Test Substance	
CAS #	Mixed Isobutyl, isooctyl and pentyl derivative
Chemical Name	Phosphorodithioic acid mixed o,o-bis(iso-Bu,isooctyl, and pentyl) esters zinc salts
Remarks	Test material purity not provided
Method	
Method/Guideline followed	OECD Guideline 402
Test Type	Acute dermal toxicity (Limit Test)
GLP (Y/N)	N
Year (Study Performed)	1984
Species/Strain	Rabbits/New Zealand White
Sex	Male and female
No. of animals/sex/group	5
Vehicle	None
Route of administration	Dermal
Dose level	2 g/kg
Dose volume	2 ml/kg
Control group included	No
Remarks field for test conditions	This study deviates from the above referenced guideline in that the dosing site was abraded prior to treatment. This was not considered a significant deviation from the guideline. Approximately 24 hours prior to topical application of the test material, the hair of each animal was closely clipped. Immediately prior to dosing the skin was abraded. A single dose of 2 g/kg of the undiluted test material was administered dermally to five male and female animals. The test material was kept in contact with the skin for a period of 24 consecutive hours under a gauze and elastic bandage. The application site was wiped clean of residual test material at the end of the 24-hour exposure period. The animals were observed for abnormal clinical signs frequently on the day of dosing and once daily for 14 days after treatment. Individual body weights were recorded on the day of dosing. The surviving animals were euthanized at the conclusion of the observation period. Gross necropsies were performed on all animals on Day 14.
Results	LD50 > 2.0 g/kg (males and females)
Remarks	No mortality was observed. Clinical signs observed in all animals included cyanosis and decreased motor activity. The majority of animals exhibited motor incoordination. Four animals exhibited a loss

	of righting reflex. Recovery from most of these signs occurred by day three post treatment. Dermal findings included necrosis, edema and ulceration. Dermal irritation persisted through study termination. Gross pathological findings were limited to pitted kidneys in one female.
Conclusions	The test article, when administered dermally as received to 5 male and 5 female New Zealand white rabbits had an acute dermal LD50 of greater than 2.0 g/kg.
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 7/13/00 (RTA-048)

1.2 Acute Inhalation Toxicity

Test Substance	
CAS #	Mixed Isobutyl, isooctyl and pentyl derivative
Chemical Name	Phosphorodithioic acid mixed o,o-bis(iso-Bu,isooctyl, and pentyl) esters zinc salts
Purity	Not Provided
Method	
Method/Guideline followed	OECD Guideline 403
Test Type	Acute Inhalation toxicity (Limit Test)
GLP (Y/N)	N
Year (Study Performed)	1986
Species/Strain	Rats/Sprague-Dawley
Sex	Male and female
No. of animals/sex	5
Vehicle	None
Route of administration	Vapor inhalation (single 4 hour whole body exposure)
Dose level	0.198 mg/L which included 74.2 ppm H_2S (actual maximum attainable concentration)
Vehicle control group	No
Chamber analysis	Yes (for hydrogen sulfide)
Remarks field for test conditions	One group of five rats/sex was exposed for 4 hours to the test material as a vapor generated by a glass distillation column filled with glass beads and heated to approximately 100°C. The distillation column was attached to a 3-neck flask. Test material was pumped into the top of the column. A portion of test material was vaporized and generated an atmosphere containing H_2S, among other possible vapors. The vapor was delivered into a 70-liter glass exposure chamber. The actual exposure concentration of H_2S as measured by gas chromatography was 74.2 ppm. The nominal concentration of the test material in the atmosphere was 0.198 mg/L. Animal observations for toxicological signs and mortality were recorded periodically during exposure and at least once daily during the 14 day observation period. Individual body weights were recorded on Day1 (immediately prior to exposure) and on Days 7 and 14. Serum cholinesterase evaluations were performed on all animals approximately 18 hours before and 30 minutes following exposure. Animals were sacrificed and subjected to a complete gross necropsy following the 14-day observation period.
Results	LC50 > 0.198 mg/L which included 74.2 ppm H_2S (maximum attainable concentration)
Remarks	All animals survived the exposure and observation periods. Lacrimation was recorded in two animals during exposure. Salivation, redness around the nose and discoloration around the mouth were observed following exposure. All animals appeared normal by day 8. All animals gained weight during the two-week study period. Serum

	cholinesterase values were variable and did not exhibit a consistent effect of test material exposure. One female exhibited gray lungs at necropsy. There were no abnormal postmortem findings evident in any of the other animals at study termination.
Conclusions	Following 4-hour whole body exposure to the test material vapor the LC50 in male and female Sprague Dawley rats was >0.198 mg/L which included 74.2 ppm H_2S. This was the maximum concentration attainable.
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 7/1400 (RTA-050)